



Neurological manifestations of COVID-19: a review of what we know so far

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Abstract

Coronavirus disease 2019 (COVID-19) has become a pandemic disease globally. While it mostly presents with respiratory symptoms, it has already been found that it could manifest with a series of neurological symptoms as well, either at presentation or during the course of the disease. Symptoms vary from non-specific such as headache or dizziness to more specific such as convulsions and cerebrovascular disease (CVD). This study aims to give an overview of the neurological manifestations of COVID-19 and discuss the potential pathogenetic mechanisms of central nervous system (CNS) involvement. Clinicians and especially internists, neurologists, and infectious disease specialists should be aware of these symptoms and able to recognize them early. Prompt diagnosis and immediate management of the neurological manifestations of the novel coronavirus will not only improve the prognosis of COVID-19 patients but will also prevent the dissemination of the disease due to misdiagnosed cases.

Keywords COVID-19 · Coronavirus · SARS-CoV-2 · Neurological manifestations · Neurology

Introduction

Coronavirus Disease 2019 (COVID-19) epidemic emerged in December 2019 in Wuhan, China and has rapidly spread to the rest of the world. The outbreak has been declared a world pandemic by WHO on 11 March 2020, with more than 2,500,000 cases worldwide so far [1]. COVID-19 is confirmed to be caused by a novel coronavirus (2019 novel coronavirus, 2019-nCoV) and presents with symptoms similar to those of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003. Both viruses shared the same receptor, angiotensin-converting enzyme 2 (ACE2) [2], thus, the novel virus was named SARS-CoV-2.

COVID-19 typically presents with fever and respiratory symptoms including dry cough and dyspnea. The elderly population is more likely to develop severe disease complications, especially those with comorbidities such as hypertension, diabetes mellitus, and chronic obstructive pulmonary disease (COPD). However, neurological manifestations of the novel coronavirus are not precepted by all clinicians,

thus, leading to inappropriate management of COVID-19 patients presenting with non-specific neurological symptoms initially. This article aims to review the cases, which reported neurological symptoms at presentation or during the course of the disease and discuss the potential mechanisms of Central Nervous System (CNS) involvement in COVID-19.

SARS-CoV-2 overview

Coronaviruses (CoVs) have an average diameter of 100 nm, and they are spherical or oval. They are enveloped viruses with a single-strand, positive sense RNA-genome. The SARS-related coronaviruses are covered by spike proteins and when observed in the electron microscopy they have a typical crown-like shape. Spike proteins contain a variable receptor-binding domain (RBD), which binds to angiotensin-converting enzyme-2 (ACE-2) receptor found in the heart, lungs, kidneys, and gastrointestinal tract, thus, facilitating viral entry into target cells [2, 4].

SARS-CoV-2, along with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), is among the seven known coronaviruses that can infect humans with a genome length of 29,000 nucleotide bases, which preserve

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the genetic information for its reproduction. The genetic similarity between SARS-CoV-2 and bat coronavirus is 96% whilst its genetic similarity with SARS-CoV is 79.5% [4]. Therefore, it is believed that the novel coronavirus originated from bats and after mutating, it infected other animals and humans. Malayan pangolin is considered the intermediate host of SARS-CoV-2 [5].

SARS-CoV-2 is thought to be transmitted most readily by respiratory droplets. Moreover, the digestive tract might be another transmission route as the virus has been detected in human stool [6]. Additionally, it is believed that it can be transmitted through aerosols under prolonged exposure, in a closed environment.

Neurological manifestations of COVID-19

Encephalitis–meningitis

Two cases of Sars-CoV-2-related encephalitis have been reported so far [7, 8]. The first one, is a 24-year-old man in Yamanashi, Japan, who initially complained about headaches, fever, and fatigue. He was prescribed antipyretic agents and laninamivir under the diagnosis of influenza and was advised to stay home. However, a few days later he was found unconscious and was transferred to the hospital, where he presented with generalized seizures, Glasgow coma scale (GCS) of 6 and neck stiffness. Brain magnetic resonance imaging (MRI) showed hyperintensity along the wall of the inferior horn of the right lateral ventricle and hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy in diffusion-weighted images (DWI) and fluid-attenuated inversion recovery images (FLAIR), indicating right lateral ventriculitis and encephalitis mainly on right mesial lobe and hippocampus. Although the specific SARS-CoV-2 RNA was not detected in the nasopharyngeal swab, it was detected in CSF confirming the diagnosis of Meningitis/Encephalitis associated with SARS-Coronavirus-2. The other case was reported in Ditan Hospital, Beijing, China, where a 56-year-old patient diagnosed with COVID-19 developed an altered level of consciousness. Although he had normal brain computerized tomography (CT) scans, cerebrospinal fluid (CSF) testing for SARS-CoV-2 was positive, confirming the diagnosis of encephalitis due to the novel coronavirus.

Encephalopathy

The first case was reported in Detroit, Miami, and is about a female airline worker in her late fifties presented with a 3-day history of cough, fever, and altered mental status [9]. She was diagnosed with COVID-19 through the detection

of the RNA of the novel coronavirus in the nasopharyngeal swab. However, due to a traumatic lumbar puncture, CSF testing for SARS-CoV-2 was unable to be performed. Non-contrast brain CT scan demonstrated symmetric hypoattenuation within the bilateral medial thalami. Brain MRI demonstrated hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions. Clinical presentation and imaging findings were consistent with the diagnosis of acute necrotizing encephalopathy (ANE), a rare complication of influenza and other viral infections, which has been related to intracranial cytokine storms, resulting in blood–brain-barrier breakdown [10]. The patient was treated with intravenous immunoglobulin. The second case concerns a 74-year-old patient, presented at the emergency department (ED) with fever and cough, who was initially discharged home with oral antibiotics [11]. He returned to the ED within 24 h with worsening symptoms, including headache, altered mental status, fever, and cough. Upon examination, the patient was found encephalopathic, nonverbal, and unable to follow any commands. Non-contrast, brain CT scan showed no acute abnormalities whilst electroencephalography (EEG) showed bilateral slowing and focal slowing in the left temporal region with sharply countered waves. The patient was found to be positive for COVID-19 (nasopharyngeal swab), whilst CSF testing did not reveal a central nervous system infection.

Cerebrovascular disease

Two studies have been conducted so far, regarding the association of COVID-19 and cerebrovascular disease (CVD). The first one is a retrospective, observational analysis of consecutive COVID-19 patients admitted to Union Hospital, Wuhan, China [12]. It showed that CVD is not uncommon during SARS-CoV-2 infection, especially in older patients with risk factors. More specifically, 5% of the patients developed acute ischemic stroke, 0.5% cerebral venous sinus thrombosis, and 0.5% cerebral hemorrhage. Patients who developed CVD were more likely to present with severe COVID-19, and to have cardiovascular risk factors such as hypertension, diabetes, and previous medical history of CVD. The other study is a retrospective case series in Wuhan, China, which reported the neurological symptoms of COVID-19 patients [13]. It showed that patients with severe COVID-19 were more likely to develop CVD as compared with non-severe cases. (5.7%—four cases of acute ischemic stroke and one case of cerebral hemorrhage vs. 0.8%—one patient with ischemic stroke). However, we should mention that both studies were conducted in Wuhan, China, thus, findings cannot be applied to the general population.

Olfactory and gustatory disorders

It is well-known that viral infections including coronaviruses can lead to smell dysfunction [14, 15]. Post-viral anosmia is one of the leading causes of loss of sense of smell in adults, accounting for up to 40% cases of anosmia [16]. The underlying cause is primarily mucosal congestion, which leads to nasal obstruction and conductive olfactory loss [16]. However, the novel coronavirus is thought to cause olfactory and gustatory disorders without causing rhinorrhea or nasal obstruction. A multi-center European study showed that 85.6% and 88.8% of COVID-19 patients developed olfactory and gustatory disorders respectively [17]. Regarding the olfactory disorders, 79.6% of the patients were anosmic and 20.4% were hyposmic. Interestingly, among the 18.2% of patients without nasal obstruction or rhinorrhea, 79.7% were hyposmic or anosmic, suggesting that the inflammatory reaction of the nasal mucosa is not the cause of smell dysfunction in this case. The gustatory dysfunction consisted of reduced, discontinued, or distorted ability to taste flavors (salty, sweet, bitter, and sour) in 78.9% and 21.1% of patients, respectively.

Other neurological symptoms

Besides the clinical manifestations mentioned before, SARS-CoV-2 can potentially present with a number of non-specific neurological symptoms. The above-mentioned clinical case series in Wuhan, China, showed that 36.4% of COVID-19 patients had neurological symptoms at onset. The most common neurological symptoms were dizziness (16.8%), headache (13.1%), skeletal muscle inflammation (10.7%), and altered mental status including confusion, disorientation, and impaired level of consciousness (14.8%) [13]. Nervous system symptoms were significantly more frequent in patients with severe COVID-19 as compared to non-severe cases (45.5% vs. (30.2%). The severity of COVID-19 was defined by the international guidelines for community-acquired pneumonia [18].

Guillain-Barré syndrome

Finally, a case of Guillain-Barré syndrome should be discussed, even though it only suggests a possible association with SARS-CoV-2 and not a proven causal relationship [19]. A 61-year-old woman without respiratory symptoms presented to the hospital with acute weakness in both legs and severe fatigue, progressing within one day. Upon examination she disclosed symmetric weakness (4/5) and areflexia in both legs and feet. Three days after admission, her symptoms progressed. Muscle strength was grade 4/5 in both arms and hands and 3/5 in both legs and feet. Sensation to light touch and pinprick was decreased distally. CSF

testing showed increased protein levels and nerve conduction studies showed delayed distal latencies and absent F waves in early course, supporting demyelinating neuropathy. The woman was diagnosed with Guillain-Barré syndrome. Seven days after admission she developed dry cough, fever (38.2 °C) and she was found to be positive for COVID-19 (nasopharyngeal swab). Although she had not initially presented with respiratory symptoms, it has been shown that sometimes SARS-CoV-2 may manifest in a non-specific way (fever in only 43.8%). Moreover, the patient's initial laboratory abnormalities (lymphocytopenia and thrombocytopenia), were consistent with the clinical characteristics of patients with COVID-19. Unfortunately, the absence of coronavirus testing on admission does not allow us to state a causal relationship between the novel coronavirus and Guillain-Barré syndrome. However, it certainly suggests that a parainfectious pattern of the syndrome may exist and neurologists should be aware of the potential association.

Discussion

As the new epidemic is still ongoing, documentation of the neurological manifestations of SARS-CoV-2 is scarce. Patients with COVID-19 may initially present with non-specific neurological symptoms including headache and dizziness. Others can develop more specific symptoms such as seizures and CVD. It has also been shown, that the more severe the infection, the more likely it is to develop neurological symptoms, especially CVD and altered mental status [13].

Human coronaviruses have already been found to be neuroinvasive and neurotropic [20, 21]. More specifically, SARS-CoV has been shown to induce various neurological diseases such as polyneuropathy, encephalitis, and aortic ischemic stroke [22]. In addition, its RNA has been detected in the CSF of a patient with the severe acute respiratory syndrome (SARS) while autopsy samples from eight patients with SARS revealed the presence of SARS-CoV in brain samples by immunohistochemistry, electron microscopy, and real-time-PCR (RT-PCR) [23, 24]. MERS-CoV is also a neuroinvasive coronavirus, which has been linked to a series of neurological manifestations including altered mental status, ischemic stroke, and Guillain-Barré syndrome [25]. The genetic and structural similarities of SARS-CoV-2 with SARS-CoV and MERS-CoV, indicate that the novel coronavirus could potentially invade CNS using the same pathophysiological mechanisms the other coronaviruses use. Although, the exact pathophysiological mechanisms are not fully understood two possible theories have been proposed so far: hematogenous dissemination and neuronal retrograde dissemination. The first one requires the presence of a given virus in the blood, where it can either infect the endothelial

cells of the blood–brain-barrier (BBB), or infect leukocytes that will become some sort of viral reservoir for dissemination to other sites [26]. On the other hand, neuronal retrograde dissemination occurs when a virus migrates by infecting sensory or motor nerve endings, achieving retrograde or anterograde neuronal transport, by using the cell machinery of active transport to access the CNS [26, 27]. Olfactory nerves and the olfactory bulb in the nasal cavity may work as a connecting channel between the nasal cavity and the CNS [28]. The latter scenario is further supported by the fact that many patients with COVID-19 experience anosmia or hyposmia [18]. Moreover, removal of the olfactory bulb in the mice resulted in a restricted invasion of CoV into the CNS [29].

Regarding the occurrence of acute cerebrovascular events, patients with severe COVID-19 are found to have increased levels of serum D-dimers, thus are more likely to develop acute embolic vascular events [30]. Also, the cytokine storm syndrome that the novel coronavirus causes, may lead to CVD as well [31]. Finally, thrombocytopenia that critically ill patients present, as well as blood pressure fluctuations in hypertensive patients due to SARS-CoV-2 binding to the ACE2 receptor may increase the risk of cerebral hemorrhage [30].

Conclusion

Although the respiratory manifestations of SARS-CoV-2 are well recognized, the neurological manifestations have not been adequately studied yet. Critically ill patients are at a greater risk of developing neurological symptoms during the course of the disease. Physicians should be aware of these symptoms and evaluate patients early to avoid the dissemination of the disease and improve the prognosis of patients. Continuing documentation of neurological symptoms and signs, timely CSF testing, EEG, and brain autopsies of COVID-19 patients who did not survive may help us understand better the neurological manifestations of the novel coronavirus as well as the pathophysiological mechanisms of CNS involvement.

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Compliance with ethical standards

Conflicts of interest Dr. P. Gklinos reports no disclosures.

References

- Mahase E (2020) Covid-19: WHO declares pandemic because of “larming levels” of spread, severity, and inaction. *BMJ* 368:1036
- Zhao Y, Zhao Z, Wang Y et al (2020) Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. *BioRxiv*. <https://doi.org/10.1101/2020.01.26.919985>
- Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, Tong S, Urbani C, Comer JA, Lim W et al (2003) A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 348:1953–1966
- Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P et al (2020) Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. *Cell Host Microbe* 27(3):325–328
- Cyranoski D (2020) Did pangolins spread the China coronavirus to people? *Nature* 2020.
- Yong Z, Cao C, Shuangli Z et al (2020) Notes from the field: isolation of 2019-nCoV from a stool specimen of a Laboratory-confirmed case of the coronavirus disease 2019 (COVID-19). *China CDC Weekly* 2:123–124
- Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M, Sakata H, Kondo K, Myose N, Nakao A, Takeda M, Haro H, Inoue O, Suzuki-Inoue K, Kubokawa K, Ogihara S, Sasaki T, Kinouchi H, Kojin H, Ito M, Onishi H, Shimizu T, Sasaki Y, Enomoto N, Ishihara H, Furuya S, Yamamoto T, Shimada S (2020) A first case of Meningitis/Encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. <https://doi.org/10.1016/j.ijid.2020.03.062>
- Xiang P, Xu XM, Gao LL, Wang HZ, Xiong HF, Li RH et al (2020) First case of 2019 novel coronavirus disease with encephalitis. *ChinaXiv* 202003:00015
- Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S (2020) Brent Griffith; COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI. *Radiology* 31:201187. <https://doi.org/10.1148/radiol.2020201187>
- Rossi A (2008) Imaging of acute disseminated encephalomyelitis. *Neuroimaging Clin* 18(1):149–161
- Filatov A, Sharma P, Hindi F et al (2020) Neurological complications of coronavirus disease (COVID-19): encephalopathy. *Cureus* 12(3):e7352. <https://doi.org/10.7759/cureus.7352>
- Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, Hong C, Chen S, Wang Y, Wang H, Li M, Jin H, Hu B (2020) Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study (3/3/2020). *Doi: 10.2139/ssrn.3550025*
- Mao L, Wang M, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Li Y, Jin H, Hu B (2020) Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *MedRxiv* 2020.02.22.20026500. *Doi: 10.1101/2020.02.22.20026500*
- Suzuki M, Saito K, Min WP, Vladau C, Toida K, Itoh H, Murakami S (2007) Identification of viruses in patients with post-viral olfactory dysfunction. *Laryngoscope* 117(2):272–277
- Van Riel D, Verdijk R, Kuiken T (2015) The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J Pathol* 235(2):277–287. <https://doi.org/10.1002/path.4461>
- Welge-Lussen A, Wolfensberger M (2006) Olfactory disorders following upper respiratory tract infections. *Taste and smell*, 63. Karger Publishers 2006:125–132
- Lechien JR, Chiesa-Estomba CM, De Siati DR et al (2020) Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. <https://doi.org/10.1007/s00405-020-05965-1>
- Zhao H, Shen D, Zhou H, Liu J, Chen S (2020) Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol*. pii: S1474-4422(20)30109-5. doi: 10.1016/S1474-4422(20)30109-5.

19. Metlay JP, Waterer GW, Long AC et al (2019) Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American Thoracic Society and Infectious Disease Society of America. *Am J Respir Crit Care Med* 200:e45–e67
20. Desforges M, Le Coupanec A, Dubeau P et al (2020) Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses* 12:14
21. Desforges M, Le Coupanec A, Brison E et al (2014) Neuroinvasive and neurotropic human respiratory coronaviruses: potential neurovirulent agents in humans. *Adv Exp Med Biol* 807:75–96
22. Tsai LK, Hsieh ST, Chang YC (2005) Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan* 14(3):113–119
23. Hung EC, Chim SS, Chan PK et al (2003) Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. *Clin Chem* 49:2108–2109
24. Gu J, Gong E, Zhang B et al (2005) Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 202(3):415–424
25. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH et al (2017) Neurological complications during treatment of middle east respiratory syndrome. *J Clin Neurol* 13(3):227–233
26. Berth SH, Leopold PL, Morfini GN (2009) Virus-induced neuronal dysfunction and degeneration. *Front Biosci* 14:5239–5259
27. Swanson PA, McGavern DB (2015) Viral diseases of the central nervous system. *Curr Opin Virol* 11:44–54
28. Koyuncu OO, Hogue IB, Enquist LW (2013) Virus infections in the nervous system. *Cell Host Microbe* 13(4):379–393. <https://doi.org/10.1016/j.chom.2013.03.010>
29. Bohmwald K, Galvez NMS, Rios M, Kalergis AM (2018) Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci* 12:386
30. Wang Y, Wang Y, Chen Y, Qin Q (2020) Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol*. 92(6):568–576
31. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395(10229):1033–1034